

## **Transannular Diels-Alder reaction on macrocycles. A general strategy for the synthesis of polycyclic compounds**

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**ABSTRACT:** Various aspects of the transannular Diels-Alder reaction are examined in order to eventually develop a general method for the synthesis of a large variety of polycyclic compounds related to the diterpenes, triterpenes and steroids. Emphasis is made on the control of the relative and absolute configuration of the polycyclic products. Preliminary work towards the synthesis of some specific target natural products is also presented.

The great contribution of R.B. Woodward and his contemporaries to the field of organic synthesis was the demonstration that organic chemists were capable of synthesizing in the laboratory highly complex organic substances. In those days, it was known that synthesis had to be carried out with functional groups, but since chemical reactivity was poorly understood, the synthetic planning had to be very general in nature, and each step had essentially to be discovered along the way by studying the reactivity of each intermediate. Later on, the reactivity of functional groups became better understood, and it became possible to put more logic in the synthetic planning. It is on that basis that E.J. Corey and his contemporaries were able to demonstrate the value of the principle of retrosynthetic analysis which is based principally on the chemical reactivity of functional groups.

Nowadays, progress in organic synthesis is presently achieved through the discoveries of new chemical reactions (methods, etc), new reaction conditions with an emphasis on asymmetric synthesis and new synthetic strategies. It is recognized that a good synthetic plan should have a high degree of control on the chemical reactivity (chemoselectivity), regioselectivity and stereoselectivity (enantio- and diastereoselectivity). Furthermore, a good plan ought to be simple minimizing as much as possible bond forming processes, and specially functional group manipulations (transformation, activation, protection and deprotection).

Returning to synthetic strategy, it is also recognized that a chemical process can be classified in three different categories. It can either be intermolecular or intramolecular in nature, and the later can be subdivided in two different ways, i.e. formation of a bond via a simple cyclization reaction or via a transannular process (ref. 1). Transannular processes ought to be very powerful synthetically. Indeed, being carried out on macrocycles, there is in such cases, a high degree of conformational restriction and as a result, proximity effects become operative and very often, these effects will increase the rate of one reaction and slow down others which are normally competing. The total synthesis of ryanodol (ref. 2) which was analyzed from the point of view of strategy, was described as one of the rare examples where transannular processes are used as key steps. In this synthesis, the formation of the required macrocycles for one of the transannular processes was produced indirectly via the cleavage of a small ring.

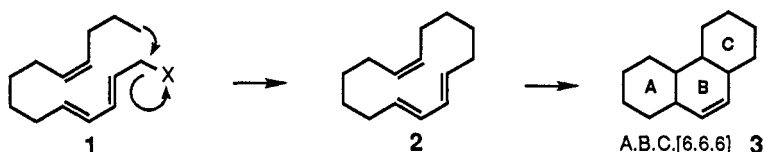
If transannular processes had not been used frequently in synthesis before it was mainly because this approach requires the use of macrocycles. However, if direct methods for the formation of large rings would become available, synthetic chemists would be in a position to develop new innovative strategies of molecular construction. Our work showed that it should be relatively easy to construct macrocycles using a simple and direct method of cyclization. One condition had however to be respected namely, the acyclic precursor should have some unsaturations appropriately located along the chain in order to cut down degrees of freedom while eliminating at the same time most of the transannular steric repulsion during the cyclization step.

Preliminary results (ref. 3) from our laboratory demonstrated that 10-membered rings could indeed be produced under medium dilution conditions via the direct displacement of an allylic or propargylic chloride

by a malonate anion. 10-Membered rings being one of the most difficult medium rings to construct directly, it should be relatively easy to construct various larger rings, and we became convinced that there was a real future for the development of new powerful synthetic strategies based on transannular reactions on macrocarbocycles. We will now describe the progress we have made in this direction.

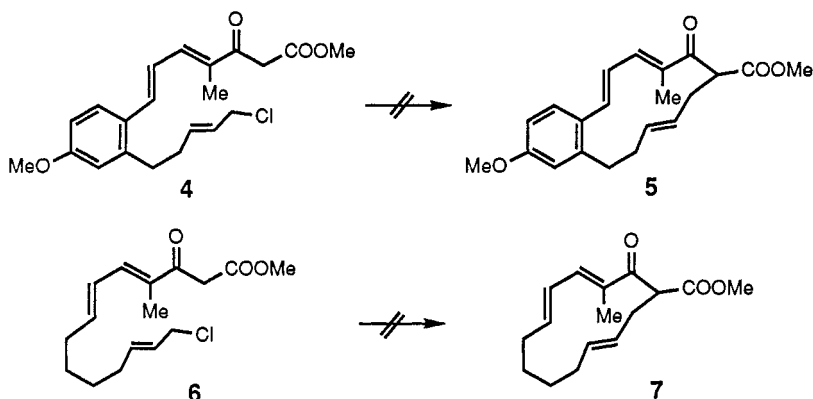
The transannular Diels-Alder reaction on macrocyclic trienes was selected as our first objective. This reaction is generally recognized as the most powerful synthetic method for the construction of carbocycles. It is also well suited for a transannular process because the two reacting species, the diene and the dienophile are neutral (not positively or negatively charged) requiring in principle only heat to undergo the Diels-Alder cycloaddition process. This study was also attractive from a synthetic point of view; in two steps from an acyclic triene ( $1 \rightarrow 2 \rightarrow 3$ ), it appeared possible to construct a tricyclic compound having four stereogenic centers and one functional group in ring B (Fig. 1).

Fig. 1



Our first two attempts in this direction met with failure because we could not induce the desired macrocyclization (ref. 4). In the first case, we constructed *trans-trans-trans* (TTT) *beta*-ketoester **4** (Fig. 2) having an allylic chloride, but could not induce its conversion into macrocycle **5**. This result was explained by the fact that the chain is probably too rigid due to conjugation and that prevented cyclization. (TTT) *Beta*-ketoester **6** which lacks the aromatic ring was then constructed and again, the desired macrocycle **7** could not be obtained; the enolate salt of **6** is still too much conjugated and the two ends of the chain cannot easily reach each other to induce the macrocyclization. We therefore decided to try the macrocyclization step on precursors which were less conjugated and were able to register our first successes.

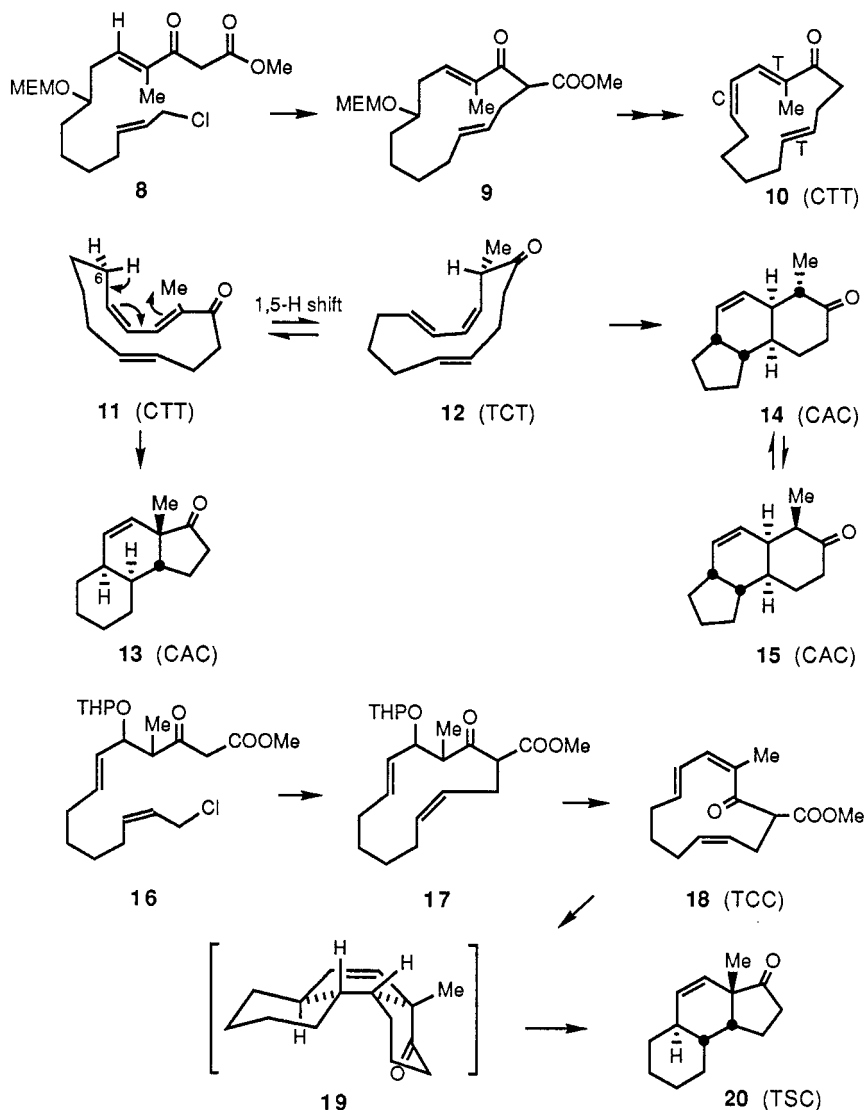
Fig. 2



The acyclic *beta*-ketoester **8** having a *trans-trans* olefin geometry was prepared (Fig. 3) and it produced ( $K_2CO_3$ , NaI, acetone) the desired macrocycle **9** in 77% yield (ref. 5). This product was then converted into the macrocyclic trienone **10** having a *cis-trans-trans* (CTT) geometry. Similarly, the other *trans-cis* acyclic *beta*-ketoester **16** (ref. 5) was prepared and converted into the macrocycle **17** (74%), which in turn was transformed into the TCC macrocyclic trienone **18**. We were then ready to attempt our first transannular Diels-Alder reactions.

On heating at  $300^\circ C$ , CTT macrocyclic trienone **10** gave a mixture of three Diels-Alder products **13**, **14** and **15** (1.8 : 2 : 1 ratio) in 90% yield. The result obtained was thus more complex than anticipated, but it could be readily explained. We had observed the formation of the expected product **13** having a *cis-anti-cis* (CAC) geometry, but molecular models revealed that this is a sterically hindered process because when the diene takes the *cisoid* geometry required for the Diels-Alder reaction (cf. **11**), there are severe steric repulsion between the methyl group and the  $C_6$  methylene group at the transition state. As a consequence, a competitive process took place starting with a 1,5 sigmatropic hydrogen migration producing a new macrocyclic trienone **12** having a TCT geometry which can then easily undergo a Diels-Alder reaction, relatively free of steric interaction, producing a tricyclic ketone **14** having a CAC geometry and a secondary methyl group. At the reaction temperature, tricyclic ketone **14** was then thermally equilibrated with the isomeric ketone **15** via their corresponding enol intermediate.

Fig. 3

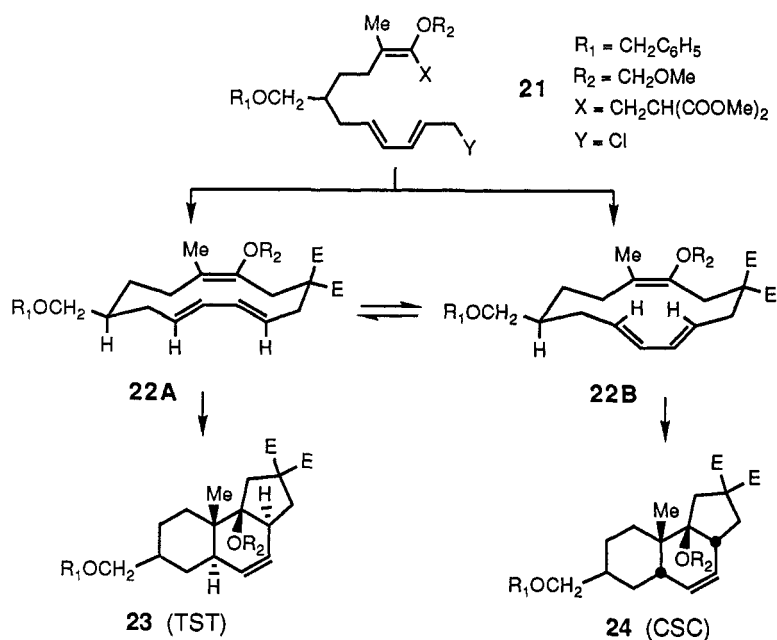


Study of the other macrocycle **18** gave better results. On heating at 300°C, TCC macrocycle **18** was cleanly transformed (90%) into the tricyclic ketone **20** by transannular Diels-Alder with concomitant decarbomethoxylation. In this case, only one product was observed simply because there is one Diels-Alder reaction which can take place without severe steric hindrance at the transition state level (cf. **19**) to produce tricyclic ketone **20** having the (*trans-syn-cis*) (TSC) geometry.

While this work was progressing, we also carried out a systematic study on direct macrocyclization affording 11 to 14 membered ring containing two unsaturations (triple and/or double bond (*cis* or *trans*)) using the displacement of allylic and propargylic chloride with a malonate. This work (ref. 6) clearly showed that the desired macrocycle is the predominant product which is formed in good yield in most cases. The next step was to verify if macrocyclization could be induced directly from an acyclic triene, using the intramolecular alkylation of a malonate with an allylic chloride.

The acyclic precursor **21** (Fig. 4) which contains a tetrasubstituted enol ether as a dienophile, a *trans-trans* diene, a malonate ester and an allylic chloride was synthesized and submitted to macrocyclization conditions (slow addition to a suspension of sodium hydride in THF-DMF at 70°C). To our surprise (ref. 7), this experiment gave directly two tricyclic products having the TST and the CSC structures **23** and **24** respectively in a 2:1 ratio. Thus, in this case, the anticipated 13-membered *trans-trans-cis* macrocyclic triene **22** could not be isolated as it underwent directly the Diels-Alder reaction. Formation of two products comes from the fact that the diene and the dienophile can react in two different manners (cf. **22A** and

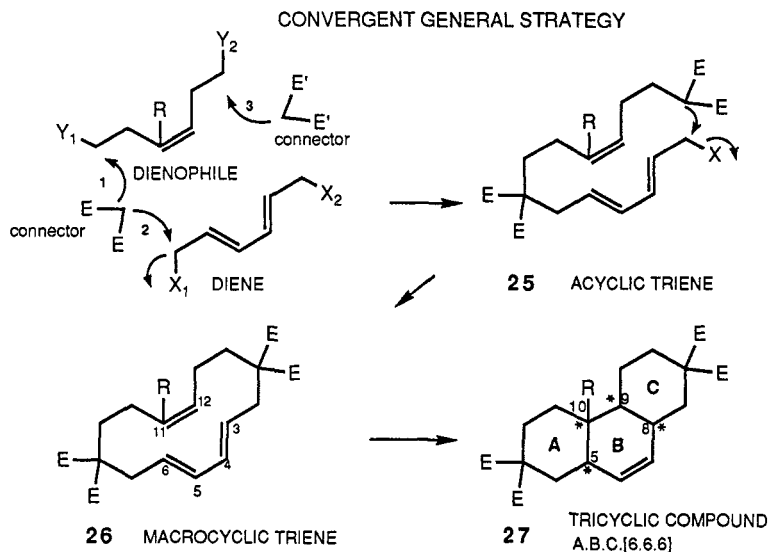
Fig. 4



**22B**). In this case, the *cisoid* conformation of the *trans-trans* diene is essentially sterically free facilitating the Diels-Alder reaction (*vide infra*), but it was felt that proximity effects due to the 13-membered ring must be the main driving force for this very facile cycloaddition. This was demonstrated by comparing the reactivity of acyclic triene **21** ( $X = \text{COOMe}$ ) with macrocyclic triene **22**. Compound **21** ( $X = \text{COOMe}$ ) should be more reactive because its dienophile is now conjugated by an ester function, however, it was found to be unreactive even when heated at  $210^\circ\text{C}$  for 10 h. Clearly, this indicated that transannular Diels-Alder represents a definite synthetic advantage as it can greatly enhance the chemical reactivity of dienes and dienophiles. As a result, the Diels-Alder reaction becomes a more general process when carried out in a transannular fashion.

Having shown that a macrocyclic triene can be constructed directly from an acyclic triene precursor, we decided to modify our general approach for the study of the synthetic potential of the transannular Diels-Alder reaction. The methods used so far for the preparation of the acyclic triene, being linear in nature, were lengthy and cumbersome. We wanted more flexibility in our approach and decided to adopt a highly convergent method using prefabricated building blocks. This method was already developed for our general study on the macrocyclization of 10 to 14-membered ring dienes. This approach is summarized in Fig. 5 and consists in assembling 4 different building blocks, a diene and a dienophile having each two potential leaving groups, and two connectors.

Fig. 5



The assembling of the macrocyclic triene is carried out in the following order. One connector is first reacted with the dienophile via a displacement reaction of an homoallylic leaving group ( $Y_1 = \text{mesylate}$ ). This is then followed by an allylic coupling reaction with the diene compound (displacement of  $X_1$ ). The homoallylic functional group in the resulting product is then converted into a good leaving group ( $Y_2 = \text{mesylate}$ ) and reacted with the second connector, producing the acyclic triene precursor **25**. The remaining allylic functional group is then activated ( $X$  is converted to an allylic chloride) in order to undergo the desired macrocyclization.

There are several advantages to this highly convergent approach. Several dienes and dienophiles having various geometries and substituents can be readily prepared and quickly assembled with the help of all sorts of connectors producing a large variety of macrocyclic trienes. The use of connectors has the additional advantage that they can play a role as substituents at the Diels-Alder stage, and more importantly, can become useful functional groups later. Interestingly, this approach provides tricyclic compounds having a functional group in each ring which can be useful for further elaboration. In principle, the connectors can also be chiral in nature, and this provides an opportunity (*vide infra*) for the induction of chirality at the Diels-Alder step yielding optically active tricyclic compounds. Thus, these connectors which can be very useful in the preparation of macrocycles, can also serve later as functional group or as device for the control of the stereoselectivity (diastereo- and enantioselectivity) during the formation of the tricyclic compounds.

In our general preliminary study, it was important to choose a connector which would not create additional chiral centers, and dimethyl malonate was chosen for both connectors. This is a versatile symmetrical connector which can be alkylated under mild conditions, yet it can be easily converted into a stereogenic center if necessary.

The next step in this project was the consideration of the relationship between geometrical isomerism of the macrocyclic triene and stereochemistry in the resulting tricycle (ref. 8). A diene can have four different configurations (TT, TC, CT and CC) and the dienophile two (C or T). The corresponding macrocyclic triene **26** can therefore have eight different configurations. For example, a TC diene with a T dienophile corresponds to a TCT configuration where the three letters refer to the unsaturations at  $C_5$ ,  $C_3$  and  $C_{11}$  respectively (cf. **26**). Tricycle **27** which has four chiral centers ( $C_5$  and  $C_{8-10}$ , steroid numbering) can exist in eight different racemic diastereoisomeric configurations (e.g. CAC, TST, etc) as indicated in Table 1.

Table 1. Predictions for the transannular Diels-Alder

Entry	Tricycle stereochemistry	Triene geometry	Tricycle stereochemistry
(1)	TAT	←* CTT →	CAC
(2)	TAT	←* TCT →	CAC
(3)	TAC	←* CCT *	CAT
(4)	TAC	← TTT →	CAT
(5)	TSC	←* CTC →	CST
(6)	TSC	← TCC *	CST
(7)	TST	←* CCC →	CSC
(8)	TST	← TTC →	CSC

On first analysis, each triene configuration can theoretically lead to two different tricyclic diastereoisomers (and their respective enantiomer). For example, triene CTT can give either tricycles TAT or CAC. However, as indicated in Table 1, it can be predicted that several transannular Diels-Alder reactions cannot take place. This is due to the fact that the Diels-Alder reaction must take place via a boat-like transition state, producing an A.B.C.[6.6.6] tricycle in which the middle ring must be in a boat conformation. Indeed, molecular models showed that because of this restriction which is stereoelectronic in nature, it is sterically impossible in some cases to reach the required chair-boat-chair transition states. For instance, due to steric reasons, tricycle TAT cannot take a conformation with ring B in a boat form, as a result, it becomes impossible to produce this compound from macrocyclic trienes CTT and TCT.

On the other hand, there are tricycles which can take two such conformations and can thus be produced from two different trienes. This is the case for tricycle CAC which can be formed from either a CTT or a TCT macrocyclic triene. There are other situations where the tricycle can take only one conformation with ring B in a boat form, these tricycles can therefore be produced from only one macrocyclic triene. For instance, TSC can be produced from triene TCC but not from triene CTC. Also, if the triene cannot take a conformation leading to a boat like transition state as required for the transannular Diels-Alder, then this reaction should not take place. This is the case for triene CCT.

In summary, the predictions for the eight triene configurations are the following: one triene (CCT) cannot undergo the transannular Diels-Alder, five trienes (CTT, TCT, CTC, TCC and CCC) can give only one racemic diastereoisomer, and two trienes (TTT and TTC) can each give theoretically two racemic diastereoisomers. Also, only one (TAT) of the eight diastereoisomeric tricycles cannot be produced directly by a transannular Diels-Alder reaction. It is also interesting to mention that *syn* and *anti* tricyclic compounds are derived from *cis* and *trans* dienophile respectively.

The next stage in our investigation was to submit these predictions to experimental verification (ref. 9). The required four dienes and two dienophiles were synthesized and assembled using dimethyl malonate to produce the eight acyclic trienes. Macrocyclization was carried out by slow addition of the acyclic trienes **25** to a solution of cesium carbonate in THF-DMF (1:1) at 80°C. The results obtained at the macrocyclization step and at the Diels-Alder stage are summarized in Table 2. Macrocycles were isolated in six cases (entries 1-3 and 5-7). In the remaining cases (TTT and TTC), tricyclic compounds rather than the expected macrocycles were directly isolated indicating that the Diels-Alder reactions took place at the temperature of macrocyclization (80°C). The mild reaction conditions for these Diels-Alder cycloadditions can be explained by the fact that in the TTT and the TTC macrocycles, the TT diene can take the required *cisoid* conformation which is devoid of steric repulsion. The other macrocycles were heated at high temperature (>300°C) in order to observe a complete thermal conversion, indicating that there is severe steric hindrance preventing the *cisoid* conformation when the diene has a CT or CC geometry.

Table 2. Macrocyclization and transannular Diels-Alder reaction

Entry	Macrocycle geometry (yield)	Diels-Alder temp. time	Tricycle stereochemistry	Ratio	Yield
1	CTT (87%)	300°C 2 h	<b>32</b> (CAC)	—	91
2	TCT (30%)	350°C 1 h	<b>32</b> (CAC) + <b>36</b> + <b>37</b>	2:3:1	>90
3	CCT (66%)	300°C 3 h	<b>38</b> + <b>32</b> (CAC) + ( <b>36</b> + <b>37</b> )	6.4:1.4:1.7	>90
4	TTT (not isolated)	80°C —	<b>56</b> (CAT) + <b>57</b> (TAC)	1:2	65%
5	CTC (81%)	300°C 2.75 h	<b>43</b> (CST)	—	89%
6	TCC (88%)	300°C 2 h	<b>46</b> (TSC)	—	100%
7	CCC (72%)	365°C 30 min	<b>43</b> (CST) + <b>46</b> (TSC)	1:1	95%
8	TTC (not isolated)	80°C —	<b>62</b> (TST)	—	53%

Macrocycle CTT **28** (Fig. 6) gave at 300°C the expected CAC tricycle **32**. Similarly, the same tricycle **32** was also obtained at 350°C from macrocycle TCT **30**, but as a mixture with two other components **35** and **36** (2:3:1 ratio). Compound **35** was shown to have an unexpected CAC tricyclic structure having the methyl group on the double bond (compound **36** could not be isolated pure and its structure is unknown). The above results can be rationalized in the following way: assuming that the Diels-Alder reaction takes place via a chair-boat-chair like transition state, molecular models clearly indicate that the methyl group creates much more steric hindrance in the CAC transition state from TCT (cf. **31**) than that from CTT (cf. **29**). As a consequence, the reaction **28** → **29** → **32** is quantitative, but not that of **30** → **31** → **32**. The formation of the unexpected tricycle **35** from macrocycle **30** can be explained by a competing transannular ene reaction producing **33** which can in turn give TCT macrocycle **34**. This compound is then easily transformed into tricycle CAC **35** because the Diels-Alder reaction is no more sterically hindered by the presence of the methyl group. Interestingly, the process **30** → **33** → **34** is an oxydo-reduction process where the dienophile and the diene have been mutually interconverted.

The prediction that the macrocyclic triene CCT **37** (Fig. 7) was not allowed to directly produce a tricyclic compound was supported experimentally. On heating at 300°C, triene **37** gave 10-membered bicycle **38** (64%) along with a mixture of the three products **32**, **35** and **36** previously obtained from macrocyclic trienes TCT **30**.

Fig. 6

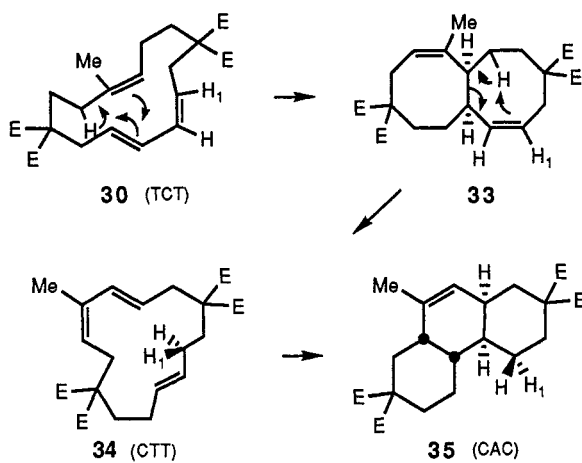
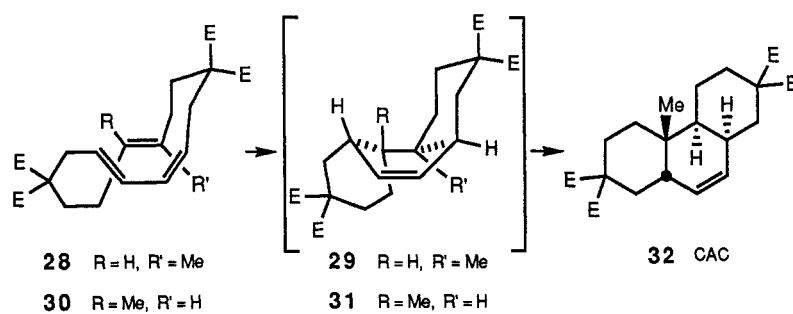
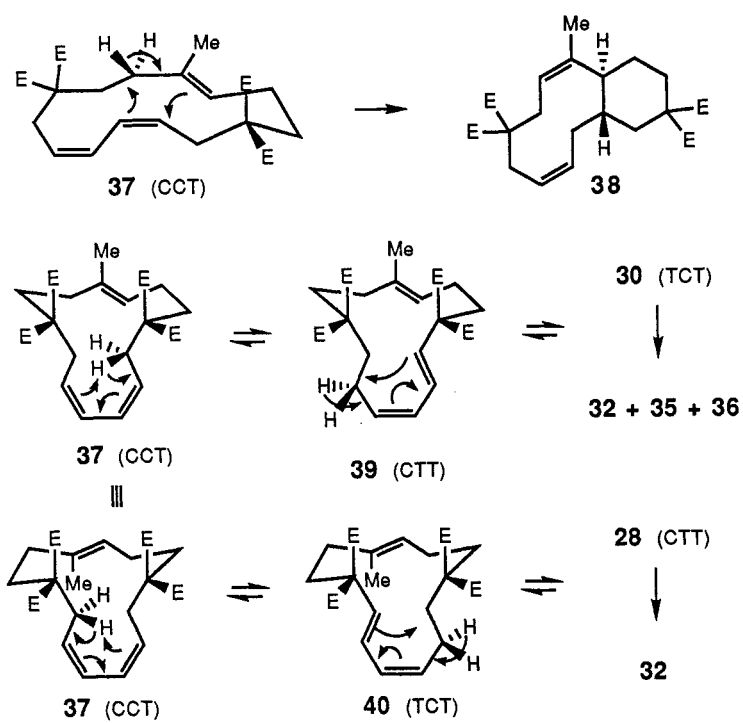


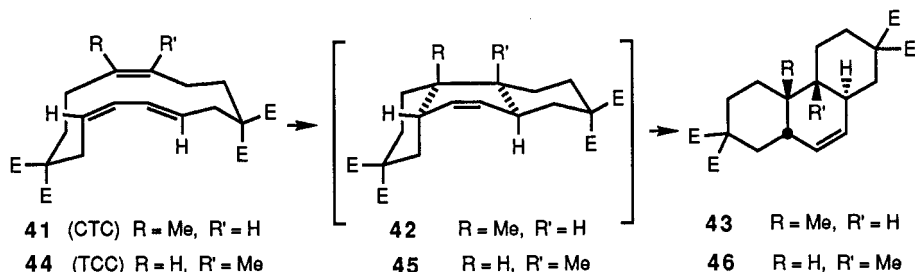
Fig. 7



The major bicyclic product **38** is formed from a transannular ene reaction from **37**. Since we know that TCT **30** gives **32** + **35** + **36** while CTT **28** gives **32**, it is reasonable to assume that macrocycle CCT **37** must have partly isomerized into a mixture of macrocyclic trienes CTT (**28**) and TCT (**30**) in order to produce the mixture of **32**, **35** and **36**. The thermal isomerization of the macrocyclic triene CCT can be explained by two consecutive 1,5 sigmatropic hydrogen migrations from **37** which can yield either macrocyclic triene TCT (**30**) or CTT (**28**) via the CTT and TCT intermediates **39** and **40** respectively. It is interesting to point out that intermediates **39** and **40** do not undergo a Diels-Alder reaction probably because they would produce tricycles having an A.B.C.[5.6.7] ring structure, the formation of which must be sterically disfavored by the seven-membered ring.

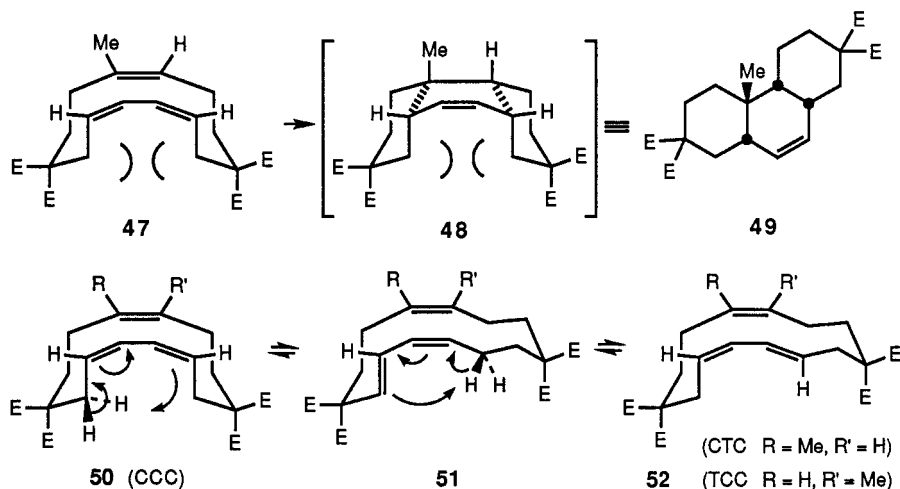
The Diels-Alder reaction of CTC and TCC macrocyclic trienes **41** and **44** (Fig. 8) went uneventful as they produced the corresponding CST and TSC stereoisomers **43** and **46** respectively as predicted, and in excellent yield. This is readily explained because both processes can take place via a chair-boat-chair like transition states devoid of severe steric repulsion as indicated in drawings **42** and **45**.

Fig. 8



CCC Macrocyclic triene **47** (Fig. 9) was predicted to give only CSC tricycle **49** via transition state **48** which appears to be quite sterically crowded. This situation is a consequence of the fact that the *cis-cis* diene is severely sterically congested when it takes the *cisoid* geometry required for the Diels-Alder reaction. Not surprisingly, on heating at 365°, none of the predicted CSC tricycle **49** was isolated, rather it produces a ~1:1 mixture of tricycles CST **43** and TSC **46**. Clearly, this indicates that the process **47** → **48** → **49** is too costly energetically, and CCC macrocycle **47** undergoes rather thermal isomerization to give a mixture of CTC and TCC macrocycles **41** and **44** which are then respectively converted into tricycle CST **43** and TSC **46**. Again, the thermal conversion of **47** into **41** and **44** can take place by two consecutive 1,5 sigmatropic hydrogen migrations (cf. **50-52**).

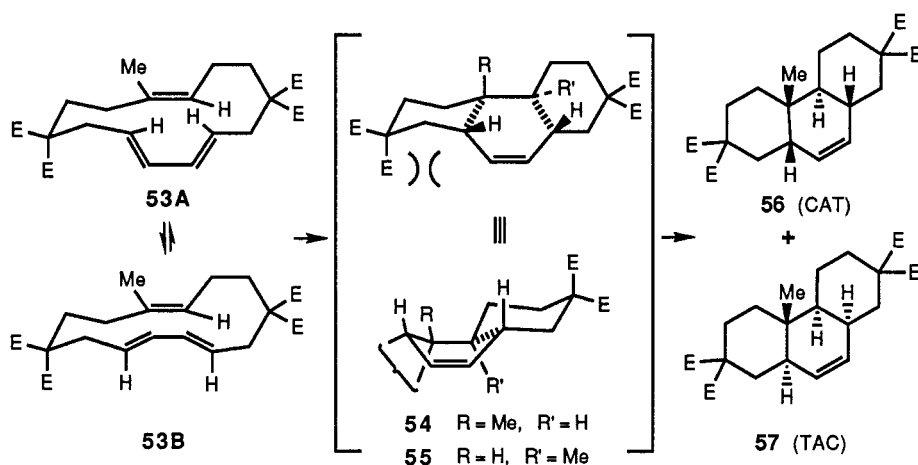
Fig. 9



As previously mentioned, the remaining macrocyclic trienes TTT and TTC were not isolated as they underwent the Diels-Alder reaction at the temperature of macrocyclization. The TTT macrocycle **53** (Fig. 10) gave a 1:2 mixture of tricycles CAT **56** and TAC **57**. This is in accord with the original prediction, since TTT macrocycle can react via conformations **53A** and **53B** to yield tricycles CAT and TAC respectively. The two competing pathways can be best compared by examining their respective transition states indicated by drawings **54** and **55**. Using this method of comparison, it can be seen that the only difference between the two competing transition states is the location of the methyl group, the rest being



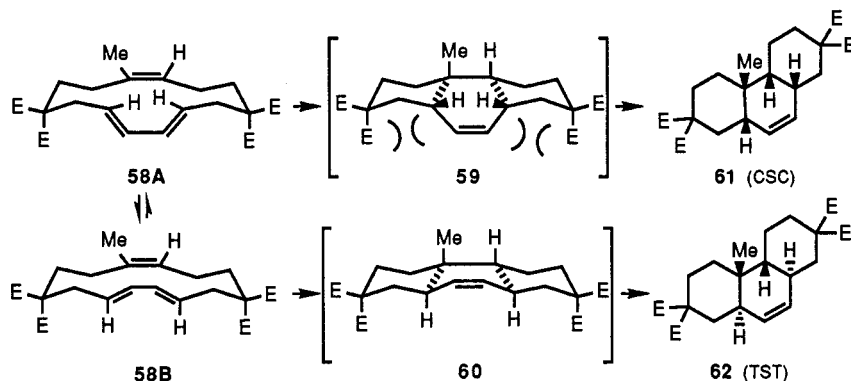
Fig. 10



identical. Molecular models show that the methyl group is sterically more crowded in transition state **55** which leads to the TAC tricycle **57**. The difference does not appear to be very large, a mixture is therefore expected, what is surprising however is that this analysis predicts a ratio where the CAT tricycle **56**, would be predominating. This is in contradiction with the experimental ratio and this topic will be rediscussed later.

TTC Macrocyclic triene gave only the TST tricycle **62** (Fig. 11) rather than the predicted mixture of CSC and TST tricycles **61** and **62**. This experimental result can be readily explained by consideration of the relative steric effect played by the ester functions. TTC Macrocycle can either react via conformation **58A** or **58B** leading to tricycles CSC **61** and TST **62** respectively. Molecular models analysis reveals that in the transition state **59** which leads to tricycle CSC **61**, there are two 1,3 diaxial type steric interactions between each pseudo axial ester function and the CH atoms of the olefin of the final product (cf. **59**). There are no equivalent interactions in the competing transition state **60**, this steric effect would therefore be the main discriminating factor favoring formation of TST tricycle **62**. The macrocyclization of TTC acyclic triene was repeated at lower temperature (45°C) and the corresponding macrocycle was isolated pure although in low yield. As anticipated, the TTC macrocyclic triene **58** was quantitatively converted into TST tricycle **62** upon reflux in benzene (ref. 10).

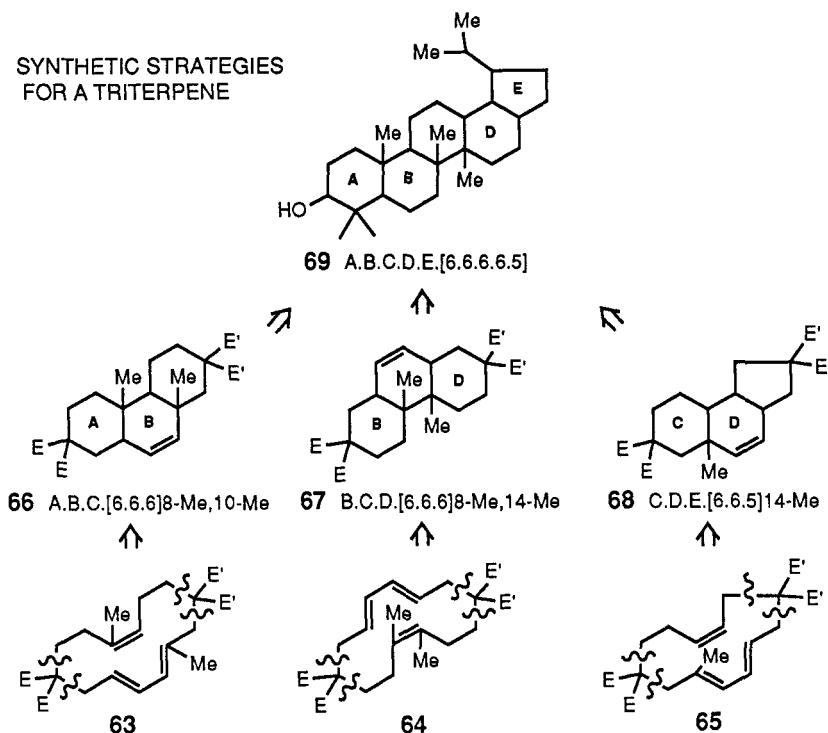
Fig. 11



In general, the results summarized in Table 2 confirm the predictions made in Table 1, the anomalous results observed (entries, 2, 7, and 8) being readily rationalized on the basis of a simple analysis at the transition state level. The global results demonstrate the power of transannular Diels-Alder reaction on macrocyclic triene for the construction of tricyclic compounds. Indeed, so far 6 of the 8 possible diastereoisomers can be obtained and the degree of stereochemical control is remarkable. The next step in this project was the evaluation of the potential of this strategy as a general method for the synthesis of polycyclic natural products.

For instance, triterpene **69** (Fig. 12) can be viewed as an A.B.C.D.E.[6.6.6.6.5]pentacyclic system which can be constructed from one of the three key tricycles **66** (A.B.C.[6.6.6]8-Me,10-Me), **67** (B.C.D.[6.6.6]8-Me,14-Me) and **68** (C.D.E.[6.6.5]14-Me). These tricycles can in turn come from the macrocyclic trienes **63**, **64** and **65** which vary in their ring size (13 and 14-membered) and the degree of

Fig. 12

SYNTHETIC STRATEGIES  
FOR A TRITERPENE

substitution on the diene and dienophile components. This type of retrosynthetic analysis can be carried out with most diterpenes, triterpenes and steroids. As a result, it can be foreseen that transannular Diels-Alder reaction on macrocycles is potentially a general method for the synthesis of most natural products belonging to these classes. In fact, this synthetic method is even more general in nature, since it does not lead only to natural products but also to polycyclic products having either varied stereochemistry for the skeleton or all sorts of substituents. Most terpenes and steroids are classified in two books (refs 11-12) Using this source of information, we have estimated that there are more than 4000 natural products which could be constructed from about 50 types of key tricyclic intermediates. Table 3 shows the number of natural products that can be made from the 20 most important tricycles.

The next objective of our investigation was clear. We had to verify if the Diels-Alder reaction would remain the predominant pathway when the diene and the dienophile are diversely substituted. We first studied the macrocyclization and subsequent Diels-Alder on macrocycles having no substituents on the diene and the dienophile (ref. 13). The macrocycles having a *cis-cis* diene were not considered as they are prone to undergo thermal isomerisation and lead to mixture of products. Four macrocycles were studied and the predicted tricyclic isomer was obtained in each case (CTT  $\rightarrow$  CAC, TTT  $\rightarrow$  CAT, CTC  $\rightarrow$  TSC and TTC  $\rightarrow$  TST). No side products were observed because the energy barrier for the Diels-Alder has not been unduly raised by the presence of alkyl substituents. Due to symmetry reasons, the TTT tricycle can only yield one isomer since the CAT and TAC stereoisomer are identical substances. The same reasoning applies for CTC (TSC=CST).

We then examined macrocycles having a tetrasubstituted unactivated dienophile bearing two methyl groups (cf. **64**  $\rightarrow$  **67**) (ref. 14). Again, four macrocycles were studied and specific formation of one stereoisomer was observed in each case (CTT  $\rightarrow$  CAC, TTT  $\rightarrow$  CAT, TTC  $\rightarrow$  TST and CTC  $\rightarrow$  CST), and it was remarkable to observe that the TTT macrocyclic triene was not isolated as it went directly to the CAT tricycle (CAT = TAC). This result is synthetically attractive because it shows that tricycles having two adjacent stereocontrolled quaternary centers can be easily constructed by this strategy. This indicates that the synthetic route (**64**  $\rightarrow$  **67**  $\rightarrow$  **69**) for the synthesis of triterpenes via a B.C.D.[6.6.6]8-Me,10-Me tricyclic intermediate should be taken seriously into account. Indeed, this could lead to a rather simple synthesis of complex triterpenoids.

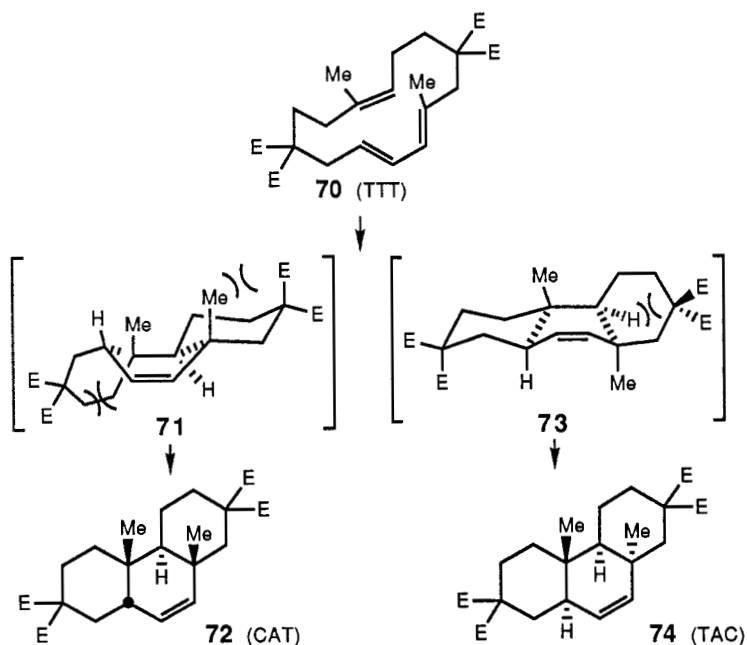
There are several natural products having alkyl groups at C<sub>8</sub> and C<sub>10</sub> (cf. A.B.C.[6.6.6]8R,10R, Table 3), therefore, macrocyclization and Diels-Alder reaction were undertaken with dienes and dienophiles having each one methyl group. Six different macrocycles (**63**) were studied (ref. 15) and it is worth noticing that all macrocyclizations were carried out in good yield (57-93%). In this series, it was possible to isolate the macrocycles having a TT diene because the presence of a methyl group on the diene generates enough steric

Table 3. Key tricyclic structures recognized in various natural products

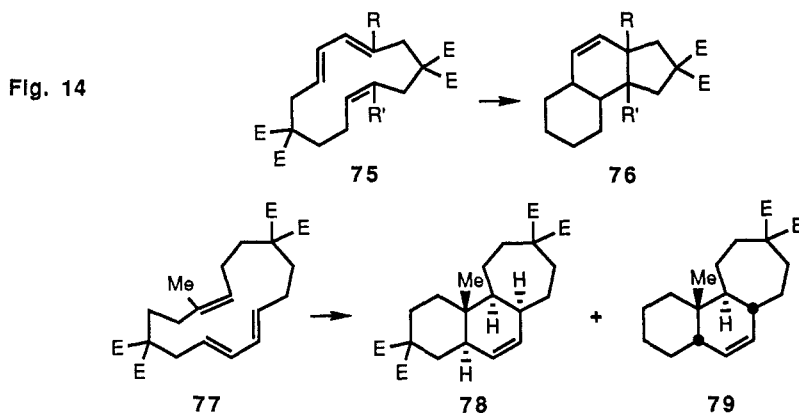
Key tricycles (position of substituents) (steroid numbering)	Number of natural products	Key tricycles	Number of natural products
<b>A.B.C.[6.6.6]</b>		<b>B.C.D.[6.6.5]</b>	
5R,10R	70	8R,13R	70
8R,10R	700	8R,14R	76
9R	40	9R,13R,14R	30
13R	1350	13R	570
		13R,14R	550
<b>A.B.C.[6.6.5]</b>		<b>C.D.E.[6.6.6]</b>	
9R,10R	25	13R,14R,17R	30
10R	17	14R,17R	200
14-oxa,8R,10R	25		
<b>B.C.D.[6.6.6]</b>		<b>C.D.E.[6.6.5]</b>	
8R,13R	32	14R,17R	41
8R,14R	280	14R,18R	17
8R,13R,14R	18		
17-oxa,8R,13R	33		

hindrance to prevent the formation of the *cisoid* conformation at the temperature of macrocyclization. Three macrocycles (TTC, TTT and TCT) gave only one stereoisomer while the others (CTT, CTC and TTC) led to mixtures. The TCC macrocycle gave as predicted only the corresponding TSC tricycle and this is readily explained on the basis of a chair-boat-chair transition state devoid of severe steric repulsion (similar to **44** → **45** → **46**). The TTT macrocycle **70** (Fig. 13) underwent the Diels-Alder reaction at 200°C producing only TAC tricycle **74**. In this case, the CAT tricycle **72** was not observed because there is one additional severe steric interaction in the corresponding transition state **71** by comparison with **73** which leads to **74**. The TCT macrocycle gave a CAC tricycle which was found to have a methyl group on the olefin as well as a secondary methyl group in ring C (ref. 15a). Thus, a process similar to the one previously described for TCT macrocycle **30** (i.e. **30** → **33** → **34** → **35** where  $H_1 = CH_3$ ) is again taking place here but with the exception that it is the major transformation. In this case, the transient formation of an intermediate equivalent to bicycle **33** having an additional methyl group **33**,  $H_1 = CH_3$ ) could be detected by NMR spectroscopy. The other three macrocycles CTT, CTC and TTC gave complex mixtures of tricycles. These mixtures were obtained because the methyl group on the diene creates additional steric interaction in the required *cisoid* conformation, and as a result, competing isomerization processes of the macrocyclic dienes took place prior to the Diels-Alder reaction. In summary, these results can be understood but details are deleted in this article.

Fig. 13



Several studies were also carried out with 13-membered macrocyclic trienes **75** (Fig. 14) which can lead to B.C.D.[6.6.5] tricycles **76** (ref. 16). Again, it would be too lengthy to discuss these results in detail. Suffice to say that the Diels-Alder reaction gave results similar to those observed with 14-membered ring, however, yields of macrocyclization were generally lower. Study of 15-membered macrocyclic trienes which can produce A.B.C.[6.6.7] tricycles was also carried out (refs 10, 17). The case of the TTT macrocycle **77** turned out to be quite interesting because this macrocycle in which the *cisoid* conformation is sterically free, was stable at room temperature. The Diels-Alder reaction which gave the expected TAC and CAT tricyclic isomers **78** and **79**, had to be carried out at 200°C. Thus one extra methylene group makes a lot of difference since the corresponding Diels-Alder reaction in the 14-membered series took place at less than 80°C. This is a clear indication that proximity effects play an important role in the case of the transannular Diels-Alder reaction. Those proximity effects are further substantiated by the fact that the corresponding TTT acyclic triene does not undergo the corresponding Diels-Alder reaction when heated at 200°C during 20 hours (ref. 10).

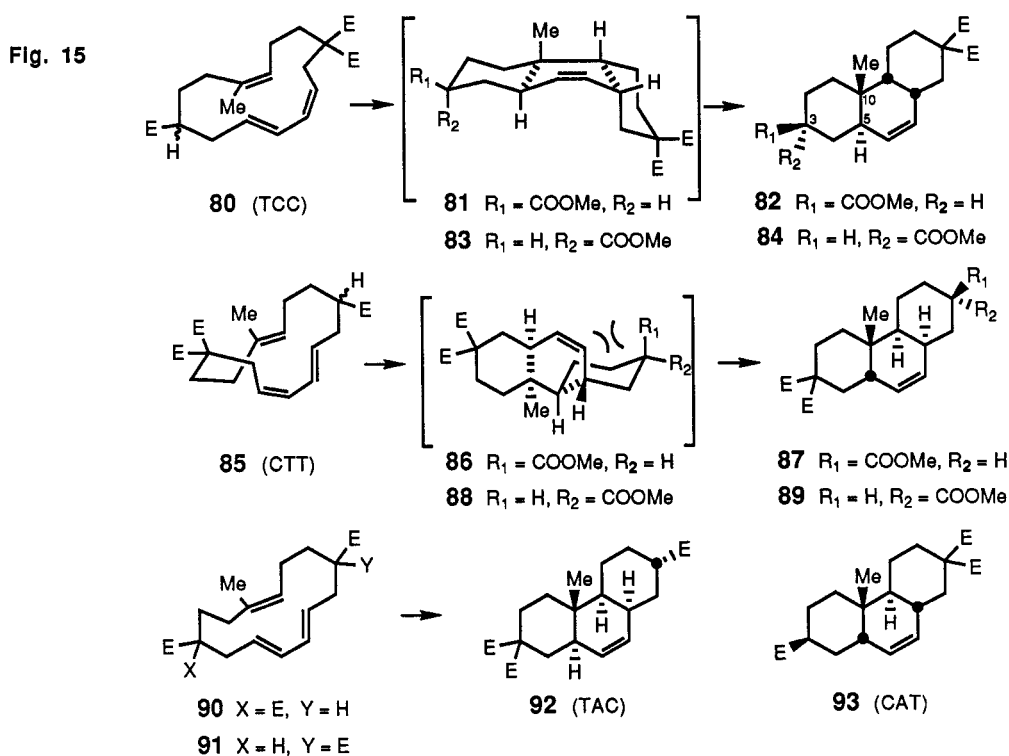


It can be concluded from the above study that transannular Diels-Alder reaction on macrocycles is a general process where ring size and alkyl substituents can be varied. It is certainly worth exploring on a synthetic point of view. The next step in the elaboration of this new general synthetic method was to start playing with another variable, i.e., the connectors, in order to see if they can be used as a device for the control of the relative as well as the absolute stereochemistry of tricycles.

The first case studied was the TCC macrocycle **80** (Fig. 15) having three ester functions which produced via **81** and **83** respectively, a 63:37 mixture of racemic TSC tricycles **82** and **84** isomeric at C<sub>3</sub> (ref. 18). This result is explained by the steric effect played by the monoester function at the transition state level. This group is equatorially oriented in **82** and axially oriented in **84**. Upon basic equilibration with sodium methoxide, an 84:16 ratio of **82** and **84** was obtained, and this indicates that at the transition state level, the axial steric interaction (cf. **83**) must be slightly less important because the C<sub>5</sub>-C<sub>10</sub> bond is not yet completely formed.

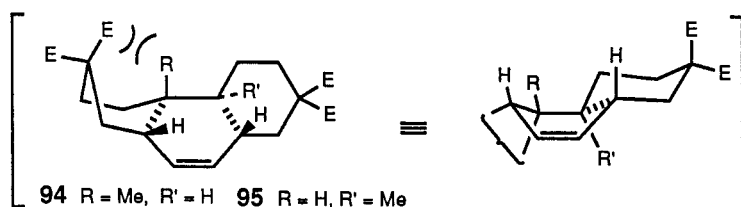
We then carried out a similar study with CTT macrocyclic triester **85** (ref. 19). Based on an analysis similar to the one just described, we expected the formation of only CAC stereoisomer **89** because in this case, the formation of the other stereoisomer requires to go through a rather severe pseudo 1,3-diaxial steric interaction which is developing between the olefinic CH atoms and the ester function (cf. **86**) at the transition state level. However, contrary to our expectation, we found out that macrocycles **85** gave a 1:4 mixture of CAC isomers **87** and **89**. This result came as a surprise because it was thought that the difference in steric effects between the two processes (cf. **86** and **88**) would be sufficient to completely eliminate the minor one. It was also a disappointment because the hope to use a chiral connector as a device to obtain a complete control of stereochemistry of the tricycle was compromised. Indeed, had we obtained only one diastereoisomer meant that starting from optically active **85** would have produced only **89** with a complete control of relative and absolute stereochemistry.

We were also hoping to use the connectors for controlling the CAT/TAC ratio in the Diels-Alder reaction of TTT macrocycles. This goal was important synthetically since there are several natural products which have either the CAT or the TAC stereochemistry. Again the results obtained were not completely satisfactory (ref. 20); the predicted product was always the major isomer (~80%) but the other possible stereoisomers were always present to some extent. For instance, **90** gave as predicted mainly the TAC stereoisomer **92** while **91** gave mainly the CAT stereoisomer **93**. However, to be really useful synthetically, 100% stereochemical control is required!



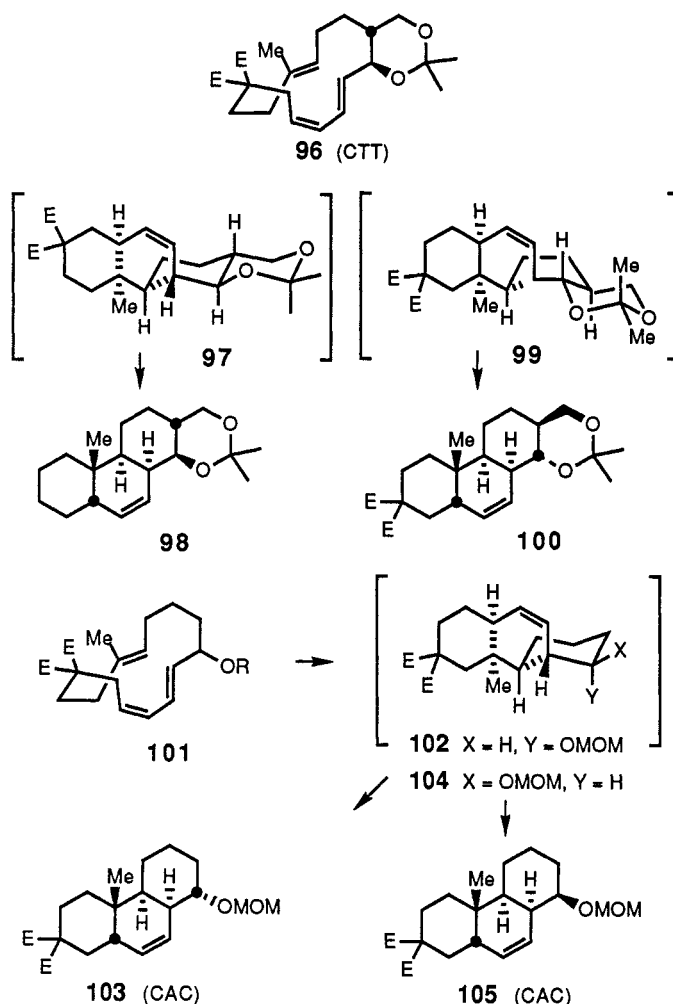
At this stage, we realized that there were several results that could not be explained completely and started to seriously question the validity of our theoretical model which was based on the assumption that the Diels-Alder reaction always take place via a chair-boat-chair like transition state. For instance, how come our theoretical model predicts the preferential formation of CAT tricycle **56** while the experiments produce a 2:1 ratio in favor of the TAC isomer **57** from TTT macrocycle **53** (Fig. 10)? It does not appear possible to invoke the influence of stereoelectronic effects since the only substituent is a methyl group. This led us to assume that the formation of tricycles CAT and TAC might take place via a boat-boat-chair rather than the normally more appealing chair-boat-chair transition states **54** and **55**. In transition states **54** and **55**, there is a severe 1,3 diaxial steric interaction between one ester function and the olefinic CH group, this interaction occurs in ring A for CAT (cf. **54**) and in ring C for TAC (cf. **55**). These steric interactions can be eliminated if the formation of CAT and TAC **56** and **57** takes place respectively from boat-boat-chair transition states **94** and **95** (Fig. 16). Moreover, these two new transition states are quite appealing because the relative ratio of the TAC and CAT tricycles **56** and **57** can be readily explained. Indeed, in **94**, the methyl group is in a boat-like conformation creating more steric hindrance than in **95** where the methyl group is in a chair-like orientation. On that basis, transition state **95** is of lower energy than **94**, and this explains why TAC tricycle is obtained as the major isomer.

Fig. 16



It is important to rigorously establish the preferred conformation of the Diels-Alder transition states, not only in order to explain the results obtained so far, but also, because this new knowledge is a prerequisite for the conception of synthetic routes with a complete control of the relative and absolute stereochemistry. Demonstration that a boat-boat-chair can compete with a chair-boat-chair transition state was realized (ref. 21) by the study of the Diels-Alder reaction of CTT macrocyclic triene **96** containing an additional acetone ring with a *trans* junction (Fig. 17). Racemic macrocycle **96** gave a 7:3 mixture of tetracycles **98** and **100**. Molecular models indicate that tetracycles **98** and **100** are respectively formed from chair-boat-

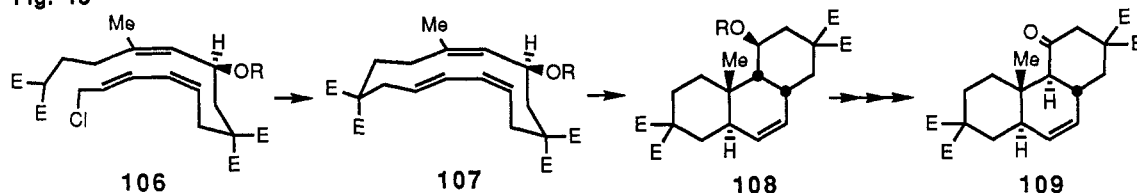
Fig. 17



chair-chair and chair-boat-boat-chair transition states **97** and **99** respectively. In this case, transition state **97** does not suffer from severe 1,3 diaxial steric interaction, it is therefore surprising a priori, to observe that transition state **99** can compete with **97**. However this situation occurs because of a stereoelectronic effect related to the presence of the C—O bond which raised induly the energy level of transition state **97**. This stereoelectronic effect was first observed (ref. 22) by studying the Diels-Alder reaction of CTT macrocyclic triene **101** having an OR group (R = methoxymethyl). This compound gave CAC tricyclic isomers **103** and **105** in 63/37 ratio indicating that the transition state **102** having an axially oriented OR group is of lower energy than that of **104** with an equatorially oriented OR group. This result is a priori surprising as it is contrastreric in nature, however it indicates that a stereoelectronic effect raising the energy of **104** must be occurring. We are suggesting that in **104**, the OR group being equatorial, is antiperiplanar to the C—C bond which is in the process of formation, overlap of the C—OR antibonding orbital with this electron poor C—C bond at the transition state must be destabilizing. As a result, the predominant formation of CAC tricyclic **103** via **102** was observed. These results further indicate that the study of transannular Diels-Alder is also interesting on a mechanistic point of view because it provides experimental information not readily available either from intermolecular or simple intramolecular studies. This is so because transannular Diels-Alder provides much better information on the precise conformation of transition states.

It was mentioned that the TAT tricycle cannot be obtained directly from a transannular Diels-Alder reaction. Since a vast number of natural products contains this relative stereochemistry, it was of interest to demonstrate that the TAT tricycle can be readily obtained from the isomerization of another tricycle. At the same time, it was also interesting to show that one chiral center on the macrocycle could induce the control of the absolute configuration of tricycles. Both these aspects were examined by the study of the optically active TCC macrocyclic triene **107** (Fig. 18) (ref. 23).

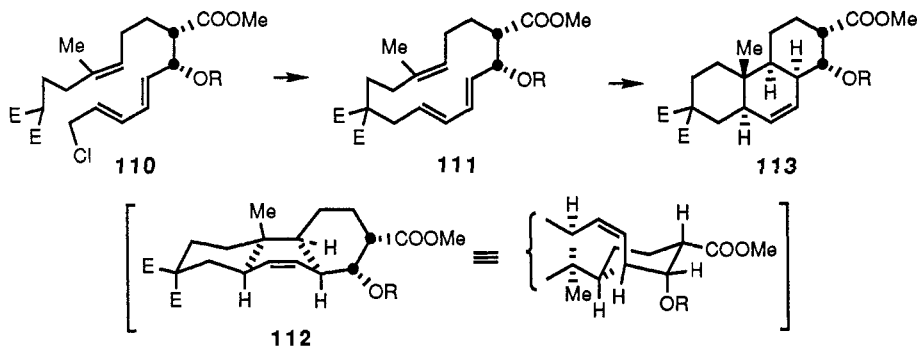
Fig. 18



The optically active *cis* dienophile having a *p*-methoxy benzyl group was prepared from L-(S)-glyceraldehyde acetonide (ref. 24) and further coupling with dimethyl malonate and the *trans-cis* diene following the general method described in Fig. 5 gave TCC allylic chloride **106** which was cyclized under the usual conditions to yield crystalline TCC macrocyclic triene **107** in 80% yield. The TCC macrocycle **107** when heated at 270°C (3 h) led to the formation of optically active TSC tricycle **108** in 85% yield after chromatography. Removal of the *p*-methoxybenzyl protecting group with DDQ, followed by oxidation (PCC) of the resulting alcohol gave a TSC tricyclic ketone which was converted by isomerization (Na<sub>2</sub>CO<sub>3</sub>, MeOH) in the more stable TAT tricyclic ketone **109**.

We have also studied several macrocycles where the diene and dienophile were first assembled by an aldol reaction. Only the most interesting cases (ref. 22) are reported here. On attempted macrocyclization at 80°C, the TTT acyclic triene **110** (Fig. 19) having a bis-sulfone (E = SO<sub>2</sub>C<sub>6</sub>H<sub>5</sub>) as a connector gave exclusively the TAC tricycle **113** in an overall yield of 90%, none of the normally competing CAT tricycle being observed. A similar result (ref. 25) was obtained with TTT acyclic triene **110** having a bis-malonate connector (E = COOCH<sub>3</sub>), which again gave only **113** but in a lower overall yield (70%).

Fig. 19

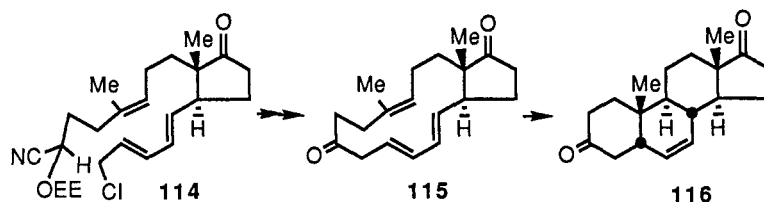


In these two cases, the Diels-Alder reaction of the transient macrocycle **111** can take place via chair-boat-chair transition state **112** which is devoid of destabilizing effects due to the appropriate orientation of the two functional groups in the newly formed ring C. Thus, the presence of these two substituents disfavors the occurrence of the chair-boat-boat competing transition state previously observed in other situations. This approach is quite interesting synthetically because the use of an asymmetric aldol coupling methodology can of course lead to optically active tricycles with a complete control of the relative and the absolute configuration. This approach is also quite appealing for future elaboration of ring C because the problem of regioselectivity is in principle solved. Indeed, having two functional groups in this ring should facilitate the direct introduction of other substituents or rings.

These last experiments indicate the general direction our laboratory is taking. Problems which need to be addressed and which are presently under investigation are the following: (a) new methods of macrocyclization, (b) discovery of connectors which would be more amenable (including the problem of regioselectivity), to further synthetic transformation once the tricycle has been produced, (c) dienophiles conjugated with a functional group to facilitate the Diels-Alder reaction and to obtain diastereoisomeric control from the *endo* rule, and (d) new solutions concerning the control of relative and absolute configuration. Last, but not the least, the most important operation is to find appropriate target molecules to be constructed in order to demonstrate the power of the transannular Diels-Alder reaction on macrocycles.

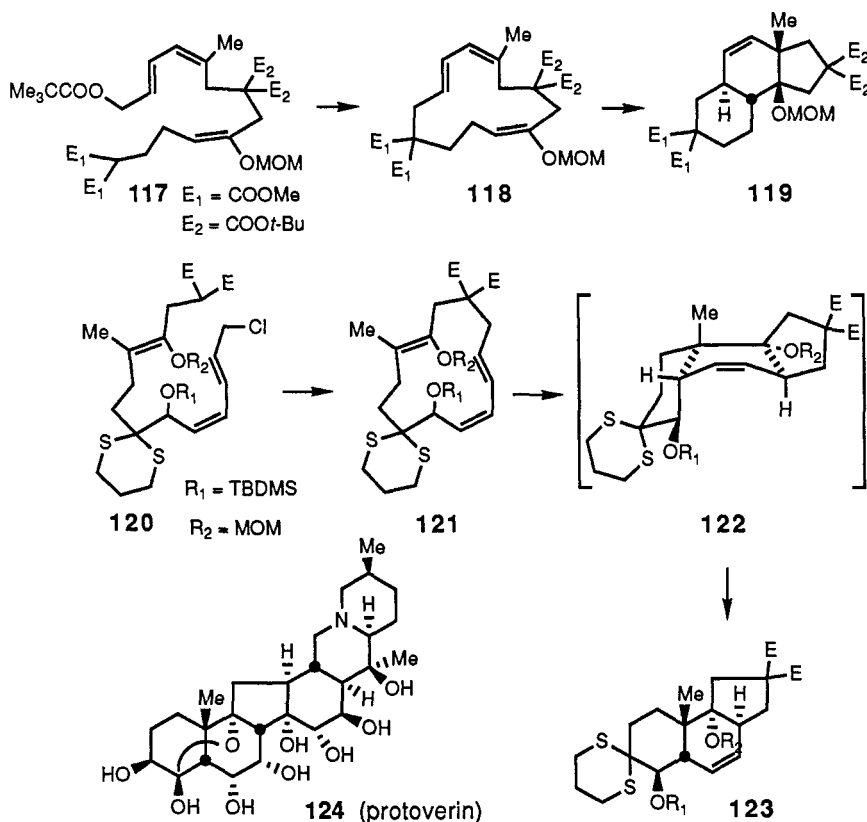
In the course of our general study, a total synthesis of a steroid derivative using the transannular strategy was reported by Takahashi and co-workers (ref. 26). The TTT acyclic precursor **114** (Fig. 20) containing a D-ring was first assembled and cyclized using ethoxyethylcyanohydrin as a connector ( $\text{LiN}(\text{TMS})_2$ ,  $80^\circ\text{C}$ ) to produce the corresponding macrocycle in 75% yield. The cyanohydrin ether was then hydrolyzed under acid conditions to produce the TTT macrocyclic ketone **115** which upon heating at  $180^\circ$  was converted into the steroid **116** (84%) having a CAT stereochemistry for the newly formed A.B.C. rings. In this case, the *trans* junction between the macrocycle and the cyclopentanone ring sterically inhibits the formation of other stereoisomers having a TAC stereochemistry.

Fig. 20



We are concluding by describing two model studies which were carried while having a specific target in mind. The first case (ref. 25) concerns the TCC acyclic triene **117** (Fig. 21) containing an allylic pivaloate which can be converted into TCC macrocyclic triene **118** in 80% yield using a palladium catalyst (ref. 27) ( $\text{O},\text{N}$ -bis(trimethylsilyl)acetamide,  $(\text{Ph}_3\text{P})_4\text{P}$ ,  $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{P}(\text{Ph})_2$ , THF). Heating **118** at  $180^\circ\text{C}$  gave TSC tricycle **119** with a B.C.D. stereochemistry corresponding to that found in 14-*beta*-hydroxysteroids. Appropriate modification of this model series should therefore lead to an interesting synthesis of cardioactive steroids. In the second case (ref. 28), the CTT acyclic triene **120** was cyclized to give CTT macrocyclic triene **121** in 75% yield. Heating **121** at  $220^\circ\text{C}$  provided via transition state **122**, CAC tricycle **123** in 76% yield after chromatography. This A.B.C.[6.6.5] tricycle can be viewed as an interesting key intermediate for the synthesis of the complex veratrum alkaloids **124**. Indeed, it has the correct ring size and functionalities required for the first three rings, and only one chiral center ( $\text{C}_8$ ) need to be corrected in order to serve as a useful key intermediate for the synthesis of this complex family of steroidal-alkaloids.

Fig. 21





Work is presently in progress in our laboratory having as a main goal the development of a general rationally designed method for the synthesis of several classes of diterpenes, triterpenes and steroids and close related products.

#### Acknowledgements

This work was carried out experimentally by my collaborators who are cited in the references. Each of them worked with dedication and it is with pleasure that I acknowledged their excellent contribution. This work was supported financially by the Natural Sciences and Engineering Research Council of Canada (NSERCC) and by the "Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (FCAR) du Québec", financial assistance from an University-Industry grant from NSERCC and Merck Frosst Center for Therapeutic Research is also acknowledged.

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